Obinutuzumab (Gazyva)

National Drug Monograph
December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the cell surface of B-lymphocytes; binding to CD20 results in B-cell death via (1) engagement of immune effector cells (2) direct cell death and/or (3) activation of complement cascade
Indication(s) Under Review in this document (may include off label)	Obinutuzumab is approved in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia.
Dosage Form(s) Under Review	Available as a 1000 mg/40 ml (25 mg/ml) single-use vial
REMS	☐ REMS ☒ No REMS *See Other Considerations for additional REMS information*
Pregnancy Rating	Likely to cause fetal B-cell depletion; may harm unborn baby

Executive Summary

Efficacy

- Obinutuzumab received FDA-approval based upon an unmet medical need among CLL patients who are elderly or have significant comorbidities.
- The combination of obinutuzumab + chlorambucil provides a treatment option for patients who are elderly or have comorbidities, who may not tolerate standard treatment regimens that contain fludarabine.
- PFS with obinutuzumab + chlorambucil provides a statistically significant benefit when compared to chlorambucil alone or the combination of rituximab + chlorambucil.

Safety

- Boxed warning highlights risk of HBV reactivation and risk of PML.
- Infusion-related reactions can be severe and life-threatening, especially with the initial dose; premedication and monitoring are necessary.
- Bone marrow suppression can be severe and prolonged; Antimicrobial prophylaxis may be considered.

Other Considerations

- Prior to initiating therapy, patients should be evaluated for risk of Tumor Lysis Syndrome (TLS) and risk for bleeding, due to expected thrombocytopenia
- At the time of publication, overall survival assessment does not indicate a benefit for obinutuzumab + chlorambucil over rituximab + chlorambucil as death rates were 8% and 12%, respectively.

Outcome in clinically significant area	O+C vs. C: PFS 26.7 vs. 11.1 mos R+C vs. C: PFS 16.3 vs. 11.1 mos O+C vs. R+C: PFS 26.7 vs. 15.2 mos
Effect Size	O+C vs. C: HR 0.18; 95% CI 0.13-0.24; p<0.001 R+C vs. C: HR 0.44; 95% CI 0.34-0.57; p<0.001 O+C vs. R+C: HR 0.39; 95% CI 0.31-0.49; p<0.001
Potential Harms	O+C: IRR 21%; neutropenia 33% R+C: neutropenia 28% C: neutropenia 27%
Net Clinical Benefit	Moderate

	Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%) Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)
Potential Impact	• Obinutuzumab + chlorambucil is a therapeutic option in previously untreated CLL patients, who are in need of therapy and are not considered appropriate for a fludarabine-based regimen.

Background

Purpose for review

FDA-approval 11/2013 with labeling revision 9/2015

Issues to be determined:
- ✔ Evidence of need
- ✔ Does obinutuzumab offer advantages to currently available alternatives?
- ✔ What safety issues need to be considered?
- ✔ Does obinutuzumab have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options[2-7]

Formulary Alternatives	Other Considerations
Chlorambucil/rituximab (C+R) vs. Chlorambucil (C)[2]	C+R vs. C: ORR 67 vs. 30%; CR 8 vs. 0%; PFS 16 vs. 11 mos; HR 0.44, 95% CI 0.34-0.57; p<0.001 OS no difference; HR 0.66, 95% CI 0.39-1.11; p=0.11 C+R vs. C: gr 3,4 neutropenia: 25 vs. 15%, infection rate 11 vs. 14%
Chlorambucil (C) vs. Fludarabine (F)[3]	C vs. F: ORR 51 vs. 72%; CR 0 vs. 7%; PFS 18 vs. 19 mos; OS 64 vs. 46 mos OS Age < 70 yrs: HR 0.7, 95% CI 0.5-0.9; OS Age > 70 yrs: HR 1.0, 95% CI 0.6-1.7; C vs. F: gr 3,4 neutropenia 23 vs. 42%; infection rate 32 vs. 26%
Non-formulary Alternative (if applicable)	**Other Considerations**
Chlorambucil/ofatumumab (C+O) vs. C[4]	C+O vs. C: ORR 82 vs. 69%; CR 14 vs. 1%; PFS 22 vs. 13 mos.; 2-yr OS: 89 vs. 87%; 3-yr OS: 85 vs. 83%
Bendamustine (B) vs. Chlorambucil[5]	C vs. B: ORR 68 vs. 31%; PFS 21 vs. 8 mos; OS no difference C vs. B: gr 3,4: neutropenia 23 vs. 10%; thrombocytopenia 12 vs. 8%; anemia 3 vs. 0%
Bendamustine/rituximab (B+R)[6]	ORR 88%; CR 23%; EFS 24 mos Gr 3,4: neutropenia 20%; thrombocytopenia 22%; anemia 20%; infection 8%
Ibrutinib (I) vs. Chlorambucil (C)[7]	I vs. C: ORR 86 vs. 35%; CR 4 vs. 2% PFS NR vs. 18.9 mos; 2-yr OS 98 vs. 85%: HR 0.16; 95% CI 0.05-0.56; p=0.001 Gr 3,4 neutropenia 10 vs. 18%

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to December 2015) using the search terms obinutuzumab and Gazyva. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Efficacy Measures (see Appendix B: Approval Endpoints)

The following outcomes are commonly evaluated in the CLL trial setting:

- Objective Response Rate (ORR)
  - Complete Response (CR), Complete Response unconfirmed (Cru)
  - Partial Response (PR), Stable Disease (SD), Progressive Disease (PD)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Duration of Response (DOR)
- Minimal Residual Disease (MRD)

Summary of efficacy findings

- The FDA approval obinutuzumab was based upon an open-label, multinational study that included previously untreated patients with CLL that required treatment (Binet Stage C or symptomatic disease) and had a Cumulative Illness Rating Scale (CIRS) > 6 (range, 0-56) or CrCl 30-69 ml/min.
- Patients were randomized 1:1:1 to chlorambucil 0.5 mg/kg PO days 1 and 15 of a 28-day cycle for a maximum of 6 cycles; chlorambucil plus obinutuzumab 1000 mg IV days 1, 8, 15 of cycle #1, then day 1 of cycles #2-6; chlorambucil plus rituximab 375 mg/m2 IV day 1 of cycle #1, 500 mg/m2 IV of day 1 of cycles #2-6
- The study population was a median age of 73 years, CrCl ~ 62 ml/min and CIRS score = 8
- Response was assessed three months following the end of treatment. The median observation time was 14.2 months and median exposure to the study medications was 6 cycles.
- Benefit noted with obinutuzumab in all subgroups except those with del (17p).
- Overall, PFS (primary endpoint) was significantly longer in the obinutuzumab arm, compared to the rituximab or chlorambucil alone arms.
- The median OS had not been reached at the time of cutoff. The rate of death at cutoff was noted to be significantly lower when obinutuzumab was compared to chlorambucil. This benefit was not significantly different from that seen with rituximab.
- Obinutuzumab induced more negative MRD status than rituximab. It is postulated that with longer follow-up, this finding will equate to longer overall survival with obinutuzumab. Although overall survival medians had not been reached at the time of publication, the rate of death was less with obinutuzumab + chlorambucil vs. chlorambucil alone.
- The dose of rituximab used in the trial has been criticized, as a dose-response relationship with rituximab monotherapy has been noted in CLL. Others counter that when combined with chemotherapy, additional benefit of high-dose rituximab is not seen. The dose used by Goede, et al. is the FDA-approved labelling of rituximab.
- Quality of life assessment via EORTC-QLQ-C30 global health scale did not indicate deterioration throughout or post-antibody therapy as compared to chlorambucil alone, which did show deterioration.

Parameter	O-C (n=333)	R-C (n=329)	C alone	
PFS	26.7 mos		11.1 mos	HR 0.18; 95% CI 0.13-0.24; p<0.001
		16.3 mos	11.1 mos	HR 0.44; 95% CI 0.34-0.57; p<0.001
	26.7 mos	15.2 mos		HR 0.39; 95% CI 0.31-0.49; p<0.001
ORR	78.2%	66.3%	33.1%	P<0.001
CR	20.7%	7.0%	0	
PR	57.7%	58.1%	54.1%	
DOR	22.4 mos	19.6 mos	9.7 mos	
MRD-negative / patients with CR, n (%)	14/69 (20%)	2/23 (9%)		
Median OS (Not reached)	NR	NR	NR	
Rate of death at cutoff	9%		20%	HR 0.41; 95% CI 0.23-0.74; p=0.002
		15%	20%	HR 0.66; 95% CI 0.39-1.11; p=0.11
	8%	12%		HR 0.66; 95% CI 0.41-1.06; p=0.08

Indirect Comparisons of Antibody + Chlorambucil Regimens in Previously Untreated CLL*

Parameter	Obinutuzumab + C vs. C[2]	Rituximab + C vs. C[2]	Ofatumumab + C vs. C[4]
Chlorambucil dose	0.5 mg/kg PO days 1 & 15, every 28 days	0.5 mg/kg PO days 1 & 15, every 28 days	10 mg/m2 PO days 1-7, every 28 days
Population	N = 781 Previously untreated; CIRS > 6 and/or CrCl < 70 ml/min Median CIRS 8 (range, 0-22) Median CrCl 62 ml/min 82% ≥ 3 comorbidities	N = 781 Previously untreated; CIRS > 6 and/or CrCl < 70 ml/min Median CIRS 8 (range, 0-22) Median CrCl 62 ml/min 82% ≥ 3 comorbidities	N=447 Previously untreated; Inappropriate for fludarabine (adv age or comorbidities) 72% ≥ 2 comorbidities 48% CrCl ≤ 70 ml/min
Age	73 yrs (range, 39-90)	73 yrs (range, 39-90)	69 yrs (range, 35-92) 69% ≥ 65 years
ECOG PS	0-1	0-1	0-2
Primary endpoint	PFS 26.7 vs. 11.1 mos; HR 0.18 (0.13-0.24); p<0.001	PFS 16.3 vs. 11.1 mos; HR 0.44 (0.34-0.57); P<0.001	PFS 22.4 vs. 13.1 mos; HR 0.57 (0.45-0.72); p<0.001
Secondary endpoints	Death rate 9 vs. 20%; HR 0.41; 0.23-0.74; p=0.002 ORR 78.2% vs. 33.1%; P<0.001 CR 28.2 vs. 0 DOR 22.4 vs. 9.7 mos	Death rate 15 vs. 20%; HR 0.66; 0.39-1.11; p=0.11 ORR 66.3% vs. 33.1%; P<0.001 CR 8.8 vs. 0 DOR 19.6 vs. 9.7 mos	ORR 82.4% vs. 68.6%; p=0.001 CR 12 vs. 1% DOR 22.1 vs. 13.2 mos
Grade 3,4 toxicity	IRR 21% Neutropenia 33% Thrombocytopenia 11%	IRR 4% Neutropenia 28%	Neutropenia 16% Thrombocytopenia 4%

* Anti-CD20 antibody/chlorambucil combinations have not been directly compared in the previously untreated population. The combinations have been directly compared to a control arm of chlorambucil alone. This chart is an indirect comparison of treatments, study population and results.

Potential Off-Label Use

Studies listed in www.clinicaltrials.gov include:

- Obinutuzumab in combination with fludarabine/cyclophosphamide or bendamustine in the first-line CLL setting
- Relapsed B-cell non-hodgkin lymphoma (NHL)
- Ibrutinib plus obinutuzumab in previously untreated and relapsed, refractory CLL setting
- Obinutuzumab plus CHOP in diffuse large B-Cell NHL
- Obinutuzumab plus CHOP or FC in relapsed/refractory follicular NHL

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• Risk of Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death • Progressive Multifocal Leukoencephalopathy (PML) resulting in death
Contraindications	• None
Warnings/Precautions	• **HBV reactivation.** HBV reactivation has been reported in patients who are hepatitis B surface antigen positive and also in patients who are HBsAg negative but are hepatitis B core antibody positive and those who appear to have resolved hepatitis B infection. All patients should be screened for HBV infection prior to starting treatment with obinutuzumab. Screening should include measuring HBsAG and anti-HBc. Those with evidence of HBV infection, a physician with

Hepatitis B expertise should be consulted regarding monitoring and consideration for antiviral therapy. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with obinutuzumab. If HBV reactivation occurs while receiving obinutuzumab, immediately stop drug with any concomitant chemotherapy and institute appropriate treatment. Insufficient data exist regarding safety of resuming therapy in those who develop HBV reactivation.

- **Progressive Multifocal Leukoencephalopathy (PML).** PML has been observed in patients treated with obinutuzumab. Discontinue obinutuzumab and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.
- **Infusion Reactions.** Severe and life-threatening infusion reactions can occur with obinutuzumab. Two thirds of patients experienced a reaction to the first 1000 mg dose. Infusion reactions can occur with subsequent infusions. Premedicate patients with acetaminophen, antihistamine and a glucocorticoid. Provide medical management as needed. Closely monitor patients during the entire infusion, as well as for the 24-hours post-infusion as reactions can occur within 24 hours of receiving obinutuzumab. Stop obinutuzumab for any Grade 4 infusion reaction. Permanently discontinue obinutuzumab therapy. For patients with Grades 3 infusion reactions, interrupt obinutuzumab until resolution of symptoms. For Grade 1 or 2 reactions, interrupt or reduce the rate of infusion and manage symptoms. Monitor patients with pre-existing cardiac or pulmonary conditions more frequently as they may be at greater risk of experiencing more severe reactions. Hypotension can present as part of an infusion reaction, therefore consider withholding antihypertensive treatments for 12 hours prior to, during and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider risk vs. benefits of withholding antihypertensive medications.
- **Tumor Lysis Syndrome (TLS).** TLS, including fatal cases, has been reported with obinutuzumab. Those with high tumor burden, high circulating lymphocyte count (>25 x 10^9/L) or renal impairment are at greatest risk for TLS and should receive appropriate TLS prophylaxis with antihyperuricemics and hydration prior to obinutuzumab infusion. During the initial days of treatment, monitor laboratory parameters of those at risk for TLS. Treatment of TLS may include the correction of electrolyte abnormalities, monitor renal function, fluid balance, administer supportive care, including dialysis as indicated.
- **Infections.** Serious bacterial, fungal and new or reactivated viral infections can occur during and following obinutuzumab therapy. Fatal infections have been reported. Do not administer to patients with an active infection. Those with a history of recurring or chronic infections may be at increased risk of infection.
- **Neutropenia.** Obinutuzumab and chlorambucil therapy resulted in Grade 3 or 4 neutropenia in 33% of patients. Neutropenia can be late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days). Antimicrobial prophylaxis is strongly recommended in patients with neutropenia during treatment. Antiviral and antifungal prophylaxis should be

considered.

- **Thrombocytopenia.** Obinutuzumab and chlorambucil therapy resulted in Grade 3 or 4 thrombocytopenia in 10% of patients. Acute thrombocytopenia occurring within 24 hours of obinutuzumab infusion was experienced by 4% of patients within the clinical trial. Fatal hemorrhage events during cycle #1 have also been reported. Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. Monitor platelet counts more frequently in patients with Grade 3 or 4 thrombocytopenia until resolution. Consider subsequent dose delays of obinutuzumab and chlorambucil or dose reductions of chlorambucil. Platelet transfusions may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.
- **Immunization.** Safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab therapy has not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery.

Safety Considerations

- Boxed warnings highlight risk of HBV reactivation. All patients should be screened for HBV infection before starting therapy. HBV-positive patients should be monitored during and after treatment.
- Boxed warning highlighting the risk of PML should alert providers to monitor and consider this diagnosis in patients presenting with new onset or changes to baseline neurological status.
- Infusion-related reactions (IRR) can be severe and occur with higher frequency with the initial doses. For all doses of obinutuzumab, ensure appropriate premedication is provided, necessary adjustments are made to the infusion rate and patient is monitored throughout infusion and for 24-hours thereafter. Grade 3 or 4 IRR occurred in 20% of those treated with obinutuzumab-chlorambucil during the first infusion. No grade 3 or 4 reactions occurred with subsequent cycles. IRR were more frequent with obinutuzumab than with rituximab.
- Assess patient for potential risk of TLS and prophylaxis with hydration and anti-hyperuricemics. Continue monitoring during risk period.
- Anticipate neutropenia and potential risk for infection. Note that neutropenia can have a late onset and can be prolonged. Consider antimicrobial, antiviral and antifungal prophylaxis.
- Evaluate concomitant therapies that can put patient at increased risk of bleed due to thrombocytopenia, especially during the first cycle.
- Severe adverse events (Grade 3, 4) occurred with greatest frequency in the obinutuzumab-chlorambucil treatment arm. Although the incidence of neutropenia was highest in this group, the incidence of grade 3-5 infections were not different among the treatment groups.

Adverse Reactions

Common adverse reactions	Most common adverse reactions (≥10%) were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea and diarrhea.
Death/Serious adverse reactions	Grade 3 or 4 reactions: infusion-related reactions 20%; neutropenia 35%; thrombocytopenia 11%; leukopenia 5%
Discontinuations due to adverse reactions	Infusion related reactions caused discontinuation in 7% of patients

Infusion Reactions. Incidence with the first infusion was 65%. Grade 3 or 4 reactions occurred in 20% with 7% of patients discontinuing therapy. Incidence of subsequent infusion-related reactions was 3% with the second 1000 mg dose and < 1% thereafter. No Grade 3 or 4 infusion reactions were reported beyond the first 1000 mg infused.

Infusion reactions were experienced by 89% of the first 53 patients on trial. Protocol modifications to include premedication with a corticosteroid, antihistamine and acetaminophen and dividing the first dose into two infusions (100 mg on day 1 and 900 mg on day 2) helped to minimize infusion reactions. After these changes were implemented, 74 patients (53%) experienced a reaction with the first 1000 mg.

Neutropenia. Incidence of neutropenia was 38% in the obinutuzumab arm and 32% in the rituximab arm. The incidence of serious adverse events was 1% and <1% respectively. Late-onset neutropenia was noted in 16% of obinutuzumab-treated patients and 12% of rituximab-treated patients.

Infection. Incidence of infection was similar between arms (38 vs. 37%, in the obinutuzumab vs. rituximab arms, respectively) with Grade 3, 4 infection rates being 11 vs. 13%, respectively. Fatal events were reported in 1% of patients in both arms.

Thrombocytopenia. Overall incidence was higher in the obinutuzmab arm vs. rituximab arm (14 vs. 7%, respectively). Events in the first cycle were higher with obinutuzumab (all grades, 11 vs. 3%; Grades 3 and 4, 8 vs. 2%). Acute thrombocytopenia was noted in 4%. Overall incidence of hemorrhage events was similar between arms. All fatal hemorrhagic events in the obinutuzumab arm occurred in cycle #1.

Tumor Lysis Syndrome. Grade 3 or 4 TLS was reported in 2 vs. 0% of obinutuzumab vs. rituximab arms, respectively.

Musculoskeletal Disorders. Adverse events related to musculoskeletal disorders were reported with a higher incidence in the obinutuzumab arm (18 vs. 15%).

Liver Enzyme Elevations. Elevated liver enzymes have occurred in the clinical trial setting. Most events occurred within 24-48 hours of the first infusion. Overall hepatotoxicity events were similar between all arms. Monitor liver function tests during treatment, especially during the first cycle. Consider interruption or discontinuation for hepatotoxicity.

The safety population included 773 previously untreated patients with CLL. The Stage 1 analysis compared obinutuzumab in combination with chlorambucil vs. chlorambucil alone and Stage 2 compared obinutuzumab in combination with chlorambucil vs. rituximab in combination with chlorambucil.

Stage 1 (obinutuzumab + chlorambucil vs. chlorambucil alone) Adverse Reactions Reported in ≥ 5%

Adverse Reaction	Obinutuzumab + chlorambucil N=241		Chlorambucil N=116	
	All grades %	Grades 3, 4 %	All grades %	Grades 3, 4 %
Infusion reactions	69	21	0	0
Neutropenia	41	35	18	16
Thrombocytopenia	15	11	8	4
Anemia	12	5	10	4
Leukopenia	7	5	0	0
Pyrexia	10	<1	7	0
Cough	10	0	7	<1
Urinary tract infection	6	2	3	<1
Back pain	5	<1	2	0

Stage 2 (obinutuzumab + chlorambucil vs. rituximab + chlorambucil) Adverse Reactions Reported in ≥ 5%

Adverse Reaction	Obinutuzumab + chlorambucil N=336		Rituximab + chlorambucil N=321	
	All grades %	Grades 3, 4 %	All grades %	Grades 3, 4 %
Infusion reactions	66	20	38	4
Neutropenia	38	33	32	28
Thrombocytopenia	14	10	7	3
Leukopenia	6	4	2	<1
Pyrexia	9	<1	7	<1
Diarrhea	10	2	8	<1
Constipation	8	0	5	0
Urinary tract infection	5	1	2	<1
Nasopharyngitis	6	<1	3	0

Stage 1: Post-baseline lab abnormalities in ≥ 5%

Adverse Reaction	Obinutuzumab + chlorambucil N=241		Chlorambucil N=116	
	All grades %	Grades 3, 4 %	All grades %	Grades 3, 4 %
Neutropenia	78	48	53	27
Lymphopenia	80	40	9	3
Leukopenia	84	37	12	<1
Hypocalcemia	38	3	33	2
Hyperkalemia	33	5	18	3
Hyponatremia	30	8	12	3
AST (SGOT incr)	29	1	16	0
Creatinine incr	30	<1	20	2
ALT (AGPT incr)	27	2	16	0
Hypoalbuminemia	23	<1	15	<1
Alk phos incr	18	0	11	0
Hypokalemia	15	1	5	<1

Stage 2: Post-baseline lab abnormalities in ≥ 5%

Adverse Reaction	Obinutuzumab + chlorambucil N=336		Rituximab + Chlorambucil N=321	
	All grades %	Grades 3, 4 %	All grades %	Grades 3, 4 %
Neutropenia	76	46	69	41
Lymphopenia	80	39	50	16
Leukopenia	84	35	62	16
Thrombocytopenia	48	13	40	8
Anemia	39	10	37	10
Hypocalcemia	37	3	32	<1
Hyperkalemia	14	1	10	<1
Hyponatremia	26	7	18	2
AST (SGOT incr)	27	2	21	<1
ALT (AGPT incr)	28	2	21	1
Hypoalbuminemia	23	<1	16	<1

Drug Interactions

Drug-Drug Interactions

- No formal drug interaction studies have been conducted.

Risk Evaluation

As of December, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	See table below

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Obinutuzumab 25 mg/ml Inj	Blinatumoma Dinutuximab Ofatumumab Omalizumab	None	None	None
Gazyva	None	None	None	Genvoya Xgeva

- (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- Total Cumulative Illness Rating Scale (CIRS) has not been validated in any cancer setting.
- There has been some debate about the doses of chlorambucil and rituximab used in the phase 3 trial.
- The combination of obinutuzumab + chlorambucil are given a category 1 recommendation from the NCCN Guidelines Version 1.2016 as first-line therapy in those with CLL without del(11q) or del(17p)/TP53 mutation AND age $\geq$ 70 years or younger patients with significant comorbidities.
- NCCN Guidelines includes obinutuzumab in all of the CLL treatment recommendations, either as category 2A or 2B.

Outcome in clinically significant area	O+C vs. C: PFS 26.7 vs. 11.1 mos R+C vs. C: PFS 16.3 vs. 11.1 mos O+C vs. R+C: PFS 26.7 vs. 15.2 mos
Effect Size	O+C vs. C: HR 0.18; 95% CI 0.13-0.24; p<0.001 R+C vs. C: HR 0.44; 95% CI 0.34-0.57; p<0.001 O+C vs. R+C: HR 0.39; 95% CI 0.31-0.49; p<0.001
Potential Harms	O+C: IRR 21%; neutropenia 33% R+C: neutropenia 28% C: neutropenia 27%
Net Clinical Benefit	Moderate

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

Recommended Dosage Regimen

- Premedicate before each infusion
- Provide prophylactic hydration and anti-hyperuricemics to patients at high risk for tumor lysis syndrome
- Administer as an intravenous infusion through a dedicated line; do not administer as IV push or bolus
- Monitor blood counts at regular intervals
- Administer by healthcare professional with appropriate medical support to manage severe infusion reactions should they occur.

Recommended Dose

- Obinutuzumab 1000 mg, intravenously [first cycle dose divided into day 1 (100 mg) and day 2 (900 mg)]
- Cycle #1 (loading doses): day 1 (100 mg), day 2 (900 mg), day 8 (1000 mg), day 15 (1000 mg)
- Cycles #2-6: day 1 (1000 mg)
- One cycle = 28 days
- Refer to package insert for full dosing information that includes recommendations for:
    - Rate of infusion
    - Infusion adjustments based upon experience of infusion reaction
    - Premedication to reduce infusion-related reactions (IRR)
    - Premedication for antimicrobial prophylaxis
    - TLS prophylaxis
    - Treatment interruption for toxicity
    - Preparation and administration

Special Populations (Adults)

	Comments
Elderly	• No differences in efficacy were observed between patients ≥ 75 years and those < 75 years. Population / SAE / AE --> death 156 ≥ 75 yrs / 72 (46%) / 11 (7%) 180 < 75 yrs / 59 (33%) / 4 (2%)
Pregnancy	• Drug is likely to cause fetal B-cell depletion based upon mechanism of action and findings from animal studies. There is no data with the use of obinutuzumab in pregnant women to inform a drug-associated risk. No embryo-toxic or teratogenic effects were observed in monkeys, but opportunistic infections and immune responses against the drug were noted. Consider the potential risk to the fetus when prescribing to a pregnant woman.
Lactation	• Benefits of breastfeeding should be considered along with the mother's clinical need for obinutuzumab, along with any potential adverse effects on the breastfed infant.
Renal Impairment	• PK analysis indicates a baseline CrCl ≥ 30 ml/min does not affect PK of obinutuzumab. Drug has not been studied in CrCl < 30 ml/min.
Hepatic Impairment	• Drug has not been studied in patients with hepatic impairment.
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting)

- Chronic Lymphocytic Leukemia (CLL) is characterized by an overgrown of lymphocytes in blood, bone marrow and lymph tissues. Approximately 15,000 new cases and 4600 deaths were attributed to CLL in 2014. There are roughly 18,000 unique Veteran patients with CLL (ICD-9 code 204.1) reported in FY2014-2015.
- CLL is primarily a diagnosis of an older population with the median age at diagnosis of 71 years. The natural history of CLL is variable; the 5-year survival rate ~ 82%.
- In the newly diagnosed population, purine analog-based therapy has been shown to improve survival in younger patients, but not in the elderly.
- Obinutuzumab is an Fc-glycoengineered humanized anti-CD20 monoclonal antibody. It recognizes type II epitope of the CD20 antigen whereas rituximab recognizes the type I epitope.

- The obinutuzumab + chlorambucil combination has been shown to improve PFS in the previously untreated CLL patient that may not be a candidate for fludarabine-based therapy. No significant difference has been noted with regard to OS.
- Severe bone marrow suppressive effects were significantly higher in the obinutuzumab + chlorambucil arm, although the rate of infections among all three treatment arms was not significantly different. The investigators did not report if the higher incidence of toxicities resulted in a greater number of hospitalizations, etc.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.